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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,734	10/01/2003	Kevin H. Gardner	UTSD:1510-1	4912

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RICHARD ARON OSMAN
SCIENCE AND TECHNOLOGY LAW GROUP
242 AVE VISTA DEL OCEANO
SAN CLEMEMTE, CA 92672

EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,734	GARDNER ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 22* is/are pending in the application.

4a) Of the above claim(s) *22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response, on June 22, 2006 to the First Action on the Merits of this case mailed April 27, 2006, is acknowledged. It is acknowledged that applicants have amended Claims 21 and 22. Claims 21 and 22 are pending. Claim 22 was previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claim 21 is hereby reconsidered.

Abstract

Objection to the Abstract filed October 13, 2005, for being a single, run-on sentence, is maintained. If Applicants wish for the text on page 3, paragraph 2, of their remarks filed July 22, 2006 to be entered as an abstract, said text should be filed on a separate page with instructions to replace the current abstract. It is noted that the Abstract comprises two paragraphs, the second of which is also a single, run-on sentence. The Abstract is herein further objected to for these two reasons.

Specification-Objections

Objection to the specification, for having two versions of the figure legends, is maintained.

Objection to the specification for having, a series of drawings is maintained. In response to this objection, Applicants argue that said drawings are "tables"; however, said drawings are not tables.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

Provisional rejection of Claim 21 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over Claim 1 of US Application 10/677,733 for the reasons stated in the prior action, is maintained. Applicants state that, upon allowance of the instant application, a terminal disclaimer will be filed.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 21 recites a method of "changing a functional surface binding specificity of a selected PAS domain...comprising the steps of: introducing into the hydrophobic core of the PAS domain a foreign ligand...". It is unclear whether the objective of said method is to (i) screen for ligands that, via binding to the hydrophobic core, alter PAS domain structure or (ii) alter PAS domain structure by contacting the domain with a ligand that is known alter the PAS domain structure by binding to its hydrophobic core. The skilled artisan would not know the metes and bounds of the recited invention. Clarification is required. For purposes of

examination, it is assumed that the objective of the method recited in Claim 21 is to screen for ligands that, via binding to the hydrophobic core, alter PAS domain structure.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claim 21 under 35 U.S.C. 112, first paragraph, lack of enablement, because the scope of Claim 21, reciting a method using any HIF2α PASB domain with any structure and any function is withdrawn. Applicants' argument that the HIF2α PASB domain is well known in the art is found to be persuasive.

Claim 21 is herein rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is enabling for a method of screening for ligands that affect the structure of the HIF2α PASB domain and then screening said ligands for binding to the hydrophibic core of said domain using the "minimum chemical shift method" of Farmer et al, 1996 (pg 18, parg 1). However, the specification is not enabling for a method of screening for ligands that affect the structure of the HIF2α PASB domain by "introducing into the hydrophobic core of the PAS domain a foreign ligand" (Claim 21, line 5). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claim 21 is so broad as to encompass a method for screening for ligands that alter the surface structure of the HIF2α PAS-B domain using any steps and any ligands that can introduce the ligand into the hydrophobic core of the PAS-B domain. The scope of this claim is not commensurate with the enablement provided by the disclosure with regard to the large number of possible steps and possible ligands that can be used to introduce the ligand into the hydrophobic core of the PAS-B domain.

The specific steps and ligands used for introducing a ligand into the hydrophobic core of the PAS domain determine the method's success. Predictability of which of the large number of possible steps and ligands to be used requires guidance with regard to how said steps and the structure of said ligands affect the desired binding. However, neither the specification nor the prior art teach the skilled artisan how to direct, restrict, or control binding of any ligand to the

hydrophobic core of any PAS domain. Therefore, the specification fails to teach "introducing into the hydrophobic core of the PAS domain a foreign ligand".

While methods for testing which steps can be used to successfully introduce a ligand into a PAS domain hydrophobic core as wells as methods for altering the structure of any ligand to determine how the structure of the ligand affects its binding to the HIF2α PAS-B hydrophobic core are known, it is not routine in the art to screen an unlimited number of steps and ligand structures to direct, restrict, or control the binding of any ligand to the PAS-B hydrophobic core, as encompassed by the instant claims. Furthermore, the steps and reagents to be used with a reasonable expectation of success in obtaining the desired binding are limited and unpredictable.

The specification does not support the broad scope of Claim 21, which encompasses any steps for introducing any ligand into the hydrophobic core of the HIF2α PAS-B domain. The specification does not support the broad scope of Claim 21 because the specification does not establish: (A) which steps can be used to direct, restrict, or control binding of any ligand into the hydrophobic core of the HIF2α PAS-B domain; (B) how any said steps can be altered or not altered and still obtain the desired binding; (C) the general tolerance of any successful method to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any steps of any method with an expectation of obtaining the desired biological function; (E) regions of any ligand's structure which may or may not be modified without effecting the desired binding activity; (F) the general tolerance of the binding activity to modification of any ligand and extent of such tolerance; (G) a rational and predictable scheme for modifying any ligand with an expectation of obtaining the desired biological function; and (H) the specification

provides insufficient guidance as to which of the essentially infinite possible choices of steps and ligands is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including using any steps and any ligands for introducing the ligand into the hydrophobic core of the HIF2α PAS-B domain. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of steps and ligands having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This claim is directed to a genus of methods, wherein one step of the method is "introducing into the hydrophobic core of the PAS domain a foreign ligand" (line 5). The specification teaches only a single representative species of such methods, wherein the ligand having the structure disclosed on page 31, upper, is used. Moreover, the specification fails to describe any other representative species of methods by any identifying characteristics or properties other than the functionality of introducing into the hydrophobic core of the PAS domain a foreign ligand. Given this lack of description of representative species encompassed

by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claim 21 under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995, for the reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(A) Based on what was known in the art, the skilled artisan would not have expected HIF2α PAS to provide a core for sensory ligand binding. Prior to the present disclosure, HIF was known to be regulated by oxygen via non-PAS mediated mechanisms only, which teaches away from any expectation that the HIF PAS domains would be sensory.

(B) Some members of the PAS family contain small cofactors within their cores, which are required for proper folding. In contrast, there is no evidence for such a cofactor within the core of the HIF2α PASB, which shows a tightly packed core with no pre-formed cavities that would suggest a binding site (Amezcua et al, 2002; Erbel et al, 2003; Morais Cabral et al, 1998).

These arguments are not found to be persuasive for the following reasons.

(A) Reply: It is acknowledged that the art teaches that non-PAS domain mediated mechanisms can regulate the response of HIF to oxygen. However, said teachings do not provide a *prima facie* case against the PAS domain also mediating an effect of oxygen, or any other ligand, on HIF. Also, see (B) below.

(B) Reply: It is acknowledged that the prior art demonstrates that some members of the PAS family contain small cofactors within their cores, which is required for proper folding. The fact that, prior to the filing of the instant invention, it had not been demonstrated that the HIF2α PAS-B domain binds a cofactor within its hydrophobic core does not provide a *prima facie* case that the HIF2α PAS-B domain does not bind a cofactor within its hydrophobic core. In fact, Amezcua et al teach that some PAS domains, containing well-packed hydrophobic cores, lacking any obvious cavities for binding of small ligands, and folding stably in a ligand-free state, are not precluded from function as sensors (pg 1358, parg 4). Amezcua et al further teach that such a domain, the PASK PAS-A domain, binds organic ligands within its core (Fig 4 pg 1358, parg 4). Amezcua et al further state that: "a very broad range of PAS domains, including those that do not copurify with ligands when isolated from natural sources, may serve sensor roles in vivo" (pg 1358, parg 5). Therefore, Amezcua et al suggest that PAS domains having a tightly packed core with no obvious pre-formed cavities, such as the HIF2α PAS-B domain, may still bind small molecules within their core and/or act as sensors.

Any teachings of Erbel et al are not relevant to the instant rejection, since Erbel et al was published after the filing date.

Morais Cabral et al do not teach that the PAS domain of their protein, the HERG K channel, has a hydrophobic core. However, they clearly state that: "we suspect that the eag

[PAS] domain will have a dynamic influence on the gating of the HERG K channel through the binding of small molecule or protein effectors" (pg 654, parg 2).

For these reasons and those presented in the prior action, rejection of Claim 21 under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995, is maintained.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
Art Unit 1656

SHERIDAN SWOPE, PH.D.
PRIMARY EXAMINER